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(54) Title: LOCAL DELIVERY OF 17-BETA ESTRADIOL FOR PREVENTING VASCULAR INTIMA HYPERPLASIA AND FOR IMPROVING VASCULAR ENDOTHELIUM FUNCTION AFTER VASCULAR INJURY

(57) Abstract: The cardioprotective effects of estrogen are well recognized. *In vitro* experiments, and upon systemic administration, 17-beta estradiol has shown to inhibit vascular smooth muscle cell proliferation and intima hyperplasia and to improve vascular endothelium function, after vascular injury. We hypothesized that locally delivered 17-beta estradiol could prevent restenosis. Compositions are use of 17-beta estradiol for *in-situ* administration at a vascular injured site are objects of the present invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/01132

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/565 A61P41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, MEDLINE, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 56312 A (SCIMED LIFE SYSTEMS INC) 17 December 1998 (1998-12-17) abstract page 7, line 5-17 page 8, line 11-18; claims 1,8,9 ---	1-6
X	YOON YOUNG-SUP ET AL: "Local intraluminal infusion of oestradiol containing liposome in rat carotid balloon injury model." EUROPEAN HEART JOURNAL, vol. 19, no. ABST. SUPPL., August 1998 (1998-08), page 616 XP001014473 XXth Congress of the European Society of Cardiology; Vienna, Austria; August 22-26, 1998 ISSN: 0195-668X abstract ---	1-6
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *P* document published prior to the international filing date but later than the priority date claimed

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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

10 September 2001

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/01132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHANG Y-Q ET AL: "EFFECTS OF GENDER AND ESTRADIOL TREATMENT ON FOCAL BRAIN ISCHEMIA" BRAIN RESEARCH, AMSTERDAM, NL, vol. 784, no. 1/2, 16 February 1998 (1998-02-16), pages 321-324, XP000884355 ISSN: 0006-8993 abstract page 322, column 1, paragraph 2; figure 2; table 1 page 323, column 2, paragraph 2 -page 324, column 1, paragraph 2	1-9
X	KAUFFMAN RAYMOND F ET AL: "Comparative effects of local vs. systemic administration of estrogen upon vascular responses to balloon injury." CIRCULATION, vol. 92, no. 8 SUPPL., 1995, page I628 XP001014766 68th Scientific Session of the American Heart Association; Anaheim, California, USA; November 13-16, 1995 ISSN: 0009-7322	1-6
Y	abstract	7-9
Y	US 5 376 652 A (JAVITT NORMAN B) 27 December 1994 (1994-12-27) abstract column 3, line 5-9 column 4, line 29-50	7-9
X	US 5 866 561 A (UNGS MARK T) 2 February 1999 (1999-02-02) abstract column 1, line 65 -column 2, line 46 column 4, line 10,11; claims 1-8	1-6
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; May 1999 (1999-05) PERROT-APPLANAT M: "Oestradiol and proliferation of vascular cells." Database accession no. PREV200000507148 XP002177140 abstract & THERAPIE (LONDON), vol. 54, no. 3, May 1999 (1999-05), pages 333-337, ISSN: 0040-5957	1-6

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INTERNATIONAL SEARCH REPORT

In tional Application No
PCI/CA 00/01132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1995 MIKKOLA TOMI ET AL: "17-beta-estradiol stimulates prostacyclin, but not endothelin-1, production in human vascular endothelial cells." Database accession no. PREV199598355996 XP002177141 abstract & JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 80, no. 6, 1995, pages 1832-1836, ISSN: 0021-972X</p> <p>---</p>	1-6
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1996 MIKKOLA TOMI ET AL: "Effect of physiological concentrations of estradiol on PGI-2 and NO in endothelial cells." Database accession no. PREV199799286811 XP002177142 abstract & MATURITAS, vol. 25, no. 2, 1996, pages 141-147, ISSN: 0378-5122</p> <p>---</p>	1-6
X,P	<p>WO 00 12147 A (SCIMED LIFE SYSTEMS INC) 9 March 2000 (2000-03-09) abstract page 4, line 29 -page 5, line 15 page 10, line 8-23 page 12, line 21-27; claims 1,11</p> <p>---</p>	1-6
X,P	<p>WO 00 10552 A (GLOBAL VASCULAR CONCEPTS INC) 2 March 2000 (2000-03-02) abstract page 1, line 10-14 page 3, line 1 -page 4, line 2; claims 1-13</p> <p>---</p> <p style="text-align: center;">-/-</p>	1-6

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/CA 00/01132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CHANDRASEKAR, BASKARAN (1) ET AL: "Coronary artery endothelial protection following local delivery of 17-beta estradiol during balloon angioplasty: A potential new pharmacological approach to improve long-term outcome of angioplasty." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY., (FEB., 2000) VOL. 35, NO. 2 SUPPL. A, PP. 58A. MEETING INFO.: 29TH ANNUAL SCIENTIFIC SESSION OF THE AMERICAN COLLEGE OF CARDIOLOGY. ANAHEIM, CALIFORNIA, USA MARCH 12-15, 2000 , XP001015229 abstract ----	1-6
X	SELMAN, CRAIG H. ET AL: "Estrogen replacement inhibits intimal hyperplasia and the accumulation and effects of transforming growth factor.beta.1" J. SURG. RES. (1998), 80(2), 380-385 , XP001014759 abstract ----	1-6
A	KEANEY J F ET AL: "17BETA-ESTRADIOL PRESERVES ENDOTHELIAL VASODILATOR FUNCTION AND LIMITS LOW-DENSITY LIPOPROTEIN OXIDATION IN HYPERCHOLESTEROLEMIC SWINE" CIRCULATION, AMERICAN HEART ASSOCIATION, DALLAS, TX, US, vol. 89, no. 5, May 1994 (1994-05), pages 2251-2259, XP001014735 ISSN: 0009-7322 the whole document ----	1-6
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1996 KUBLIK HEIKE ET AL: "Nasal absorption of 17-beta-estradiol from different cyclodextrin inclusion formulations in sheep." Database accession no. PREV199799383935 XP002177143 abstract & EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 42, no. 6, 1996, pages 320-324, ISSN: 0939-6411 -----	7-9

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

In view of the wording of claims 1-9 presently on file, in as far as the expression "derivative of 17-beta estradiol" is concerned, which renders it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely the use of and compositions/devices comprising 17-beta estradiol.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No

PCT/CA 00/01132

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9856312	A	17-12-1998	NONE
US 5376652	A	27-12-1994	AU 682084 B 18-09-1997 AU 1256895 A 19-06-1995 CA 2177822 A 08-06-1995 EP 0730457 A 11-09-1996 JP 9506091 T 17-06-1997 WO 9515165 A 08-06-1995 US 5587368 A 24-12-1996
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